Nonviral Sexually Transmitted Diseases

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Clin Colon Rectal Surg 2019;32:358–363.

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Abstract

This article provides a practical overview for the management of nonviral sexually transmitted diseases affecting the perianal and anorectal regions. Clinical manifestations, diagnosis, and treatment of syphilis, gonorrhea, chancroid, donovanosis, and lymphogranuloma venereum are individually addressed.

Keywords

- anorectal
- syphilis
- gonorrhea
- chancroid
- donovanosis
- lymphogranuloma venereum
- sexually transmitted disease

Nonviral sexually transmitted diseases are relevant in the practices of colon and rectal surgeons. These include perianal and anorectal presentations of syphilis, gonorrhea, chancroid, donovanosis, and lymphogranuloma venereum (LGV). Their manifestations are more common in other zones of the body—particularly the genital regions. Recognition of their proctologic involvement facilitates appropriate and timely treatment. Misdiagnosis permits disease progression with potentially devastating local and systemic sequela. Therefore, both the primary presentations, evaluation and management as well as their secondary and potential tertiary manifestations are discussed.

Syphilis

This sexually transmitted disease affects male more commonly than females (2:1–4:1). The spirochete *Treponema pallidum* infection causes a usually painless ulcer or chancre at the site of inoculation. There may be regional lymphadenopathy as the process becomes a systemic infection. The spectrum of manifestations includes primary, secondary, and tertiary stages if left untreated. Humans are the only natural reservoir. Spirochetes pass through intact mucous membranes and damaged skin, where they divide locally causing a host inflammatory response and chancre formation. Single or multiple lesions may be present. The primary phase of syphilis infection is the most contagious stage (►**Fig. 1**).

Spirochetes go on to migrate via the bloodstream to disseminate widely. Secondary and tertiary forms are due to this vascular invasion, where terminal arterioles are obliterated from inflammatory responses.

Transmission to a fetus is possible, even in cases of long-standing syphilis. It is rarely communicable after 4 years of latent infection or in cases of tertiary disease. Tertiary syphilis is manifested by neurologic and vascular abnormalities. The incubation period is typically 10 to 90 days—with an average of 21 days. Regional lymphadenopathy occurs within 1 week of transmission. Lymph nodes are generally rubbery, nontender, and often unilateral.

The hallmark symptoms are genital ulcers or chancre that appear at the site of inoculation. Perianal chancre is distinctly less common than genital presentations. They usually are painless, unless superinfection occurs. Chancres start as a papule that ulcerates with a raised border associated with serous exudate. The surface may become crusted. While these lesions may appear similar to chancroid (caused by gram-negative streptobacillus *Haemophilus ducreyi*), the ulcerations in the latter are most often painful and are associated with markedly tender lymphadenopathy.

The course is progressive. Even without treatment, the primary infection or chancre heals within 4 to 6 weeks. A

Issue Theme Perianal Dermatology; Guest Editors: Adrián E. Ortega, MD, FASCRS, and Xavier Delgadillo, MD, EBSQ-C

DOI https://doi.org/10.1055/s-0039-1687831.
ISSN 1531-0043.

Fig. 1 Perianal chancre presentation with multiple lesions (Photo—F. Ruiz Healy).

subsequent latent infection ensues. Untreated, it can progress to secondary and tertiary forms of the disease. Secondary syphilis occurs as a macular exanthema 2 to 6 months after primary infection and 2 to 10 weeks after the primary chancre appears. Secondary symptoms include maculopapular, papular, pustular, or acneiform lesions. They commonly involved the hands and feet—*palms and soles*. They may also occur on the torso, scalp, hairline, and neck. These lesions are usually symmetric. Condyloma lata appears as a soft, flat papule in the perineum or perianal area, but may also be seen on the axillae, mouth, or toe webs. These lesions are highly contagious. Secondary symptoms may wax and wane. The initial manifestation may be a relatively mild one, followed by recurrent eruptions a month or more afterward. Symptoms usually last for 4 to 6 weeks before spontaneous resolution, latency, and then recurrence at variable intervals.

Tertiary syphilis results from inflammatory changes in blood vessels. It is accompanied by nodular-ulcerative, crusted plaques with irregular borders on the extensor surfaces of the arms, back, or face. A gumma is a solitary nodule with punched out ulceration, which can occur anywhere but is common on the face, scalp, chest, and calf.

Identification of *T. pallidum* within tissue of lesion exudate is definitive for the diagnosis of early syphilis. Traditionally, dark field microscopy was required to reveal the characteristic findings—corkscrew organisms 5 to 20 µm in length with accordion-like contractile movements. Specimens for evaluation are obtained by debridement of the chancre crusts then cleaned with saline swabs. A scalpel is used to scrape the area and express the serous exudate when lesions are not primarily eroded or ulcerated. This exudate is used to perform dark-field microscopy. Secondary syphilis or condyloma lata lesions may also reveal the spirochetes but may require aspiration of regional lymph nodes to obtain fluid for evaluation.

Serologic tests are also available. A typical diagnostic process involves screening the patient with a nontreponemal assay—for example, the venereal disease research laboratory or rapid plasma reagin tests. These are nonspecific antibody titers that can correlate with disease activity. A fourfold increase in titers is required. However, results may remain elevated independent of treatment. They cannot always be used to assess response. These tests may not be elevated for 3 to 4 weeks following infection, limiting their usefulness in the acute setting. False-positive and false-negative results may also occur. *Treponema pallidum* particle agglutination (TP-PA) test clarifies matters further. Treponemal immunoassays are now available. These include Phoenix Biotech Trep-Sure Antibody EIA, Siemens ADVIA Centaur Syphilis Assay, and DiaSorin LIASON Treponema Assay. These tests are increasingly used in both screening and confirmatory testing algorithms. Recent studies suggest that these tests are comparable to the TP-PA test in sensitivity, specificity, and percent agreement.[1]

When testing is performed during the incubation period, retesting should be performed 2 to 4 weeks later using a nontreponemal antibody test. Nontreponemal test titers usually decline after treatment. Individuals may become nonreactive. Elevated nontreponemal antibody levels may persist without regard to disease activity.

Tertiary syphilis rarely demonstrates spirochetes. Cerebrospinal fluid evaluation may reveal abnormalities, though it may depend on which area of the brain is affected—meninges, meningovascular, or parenchymal disease. Location reflects presentation. Photophobia or neck stiffness indicates meningeal involvement. Stroke-like syndromes with focal deficits accompany meningovascular disease. Tabes dorsalis (foot drop, ataxic gait with loss of vibration, and proprioception due to demyelination) with Argyll Robertson pupils (reaction to accommodation but not to light) are seen in parenchymal disease.

The Center for Disease Control (CDC) guideline recommends 2.4 million units of intramuscular penicillin G in a single dose.[2] Alternatives for penicillin (PCN)-allergic patients include doxycycline (100 mg by mouth [PO] two times a day [BID] x 2 weeks), tetracycline (500 mg PO four times a day [QID] for 2 weeks), or erythromycin (500 mg PO QID x 2 weeks). Latent forms of syphilis (including secondary and tertiary infections) are treated with 2.4 million units PCN. Two repeat doses may be required. A total 7.2 million units are administered at 1-week intervals to ensure complete clearance of the spirochete infection. Neurosyphilis may require even higher doses.

Gonorrhea

Neisseria gonorrhoeae is a gram-negative diplococcus causing this sexually transmitted disease. Transmission may occur during asymptomatic or minimally symptomatic periods. Neonatal exposure is possible. It can also cause disseminated gonococcal infection affecting joints secondary to immune-complex formation and deposition. Strains predominately affecting the joints tend to cause minimal genital symptoms. Common presenting symptoms include urethral discharge, dysuria, and vaginal discharge. Anorectal manifestations include copious purulent discharge, proctitis, tenesmus, and rectal bleeding (►**Fig. 2**). Males having sex with males (MSM) and women may transmit the infection during oral–anal or anoreceptive intercourse. Women may also develop anorectal infections via contiguous spread from cervical or urethral infections.[3] Deeper infections may produce prostatitis,

epididymitis, salpingitis, and even peritonitis in females. Newborns can develop conjunctivitis producing corneal ulceration.

The diagnosis requires gram-negative diplococci seen on gram stain, with confirmatory culture from affected site (urethra, oropharynx, rectum, cervix). Anoscopy typically shows thick, yellowish/purulent mucoid discharge expressible from the anal crypts with gentle perianal pressure. Nonspecific proctitis may also be present. Cultures are performed with chocolate agar—Thayer-Martin medium. Nucleic acid amplification techniques are utilized to evaluate subtypes. Individuals should also be tested for syphilis, *Chlamydia*, and human immunodeficiency virus (HIV). Sexual partners should also be evaluated.[4]

Males are likely to seek medical attention soon after onset of symptoms secondary to the degree of discomfort. Transmission may occur to others prior to onset of symptoms, so that all potential sexual contacts should be screened and treated. Untreated or disseminated forms of the disease can cause tenosynovitis, septic arthritis, Fitz-Hugh-Curtis syndrome, pericarditis, meningitis, and rarely acute respiratory distress syndrome.

Dual therapy is typically recommended given the potential for antimicrobial resistance. The CDC guidelines recommend a single dose of ceftriaxone (250 mg intramuscularly) and a single dose of azithromycin 1 g PO for uncomplicated gonococcal infections of the cervix, urethra, and rectum. Administering these medications together under direct observation improves compliance. Doxycycline (100 mg PO BID for 7 days) may be substituted in cases of azithromycin allergy. Empiric treatment is recommended for patients with high suspicion for infection with exudates on rectal exam because test confirmation often requires more than 2 days.

Fig. 2 Anorectal gonorrhea with copious purulent discharge in evidence (Photo—A. Ortega).

Chancroid

Haemophilus ducreyi is a gram-negative rod producing anogenital ulceration called chancroid. This sexually transmitted infection is endemic in Africa, Latin America, and the Caribbean. Its prevalence has overall declined in the United States except for sporadic outbreaks. The disease more commonly afflicts men. It is associated with HIV infection and high-risk behaviors such as commercial sex work and drug abuse. The ulcers themselves harbor bacteria. Direct contact with broken skin allows for transmission. They appear as erythematous, shallow, irregular, and uneven lesions covered with necrotic exudate which are typically painful (►**Fig. 3**). They are associated with unilateral inguinal lymphadenopathy which may become suppurative called buboes.

Herpes anorectal infections commonly present with intense pain preceding the frank eruption of vesicles and ulcers. Syphilis produces chancres that appear as relatively nonpainful ulcerations. Chancroids are painful ulcerations associated with inguinal lymphadenopathy. Diagnosis is made by gram stain of ulcer exudates or pus expressed from lymph nodes. Gram-negative pleomorphic coccobacilli form a *school of fish* pattern.

Polymerase chain reaction (PCR) has emerged as a more sensitive and reliable testing modality. HIV and syphilis testing should be performed at the time of chancroid diagnosis. These tests are repeated in 3 months if the preliminary tests were negative.

The CDC recommends treatment with a single dose of azithromycin 1 g PO or ceftriaxone 250 mg intramuscularly. Ciprofloxacin 500 mg PO BID for 3 days or erythromycin

Fig. 3 Perianal chancroid may resemble neoplasms. The more rapid evolution of the former may help guide the diagnosis (Photo—Genital & Perianal Diseases—A Color Handbook. Mroczkowski TF, Millikan LE, Parish LC, editors. 2014 © Boca Raton, FL: CRC Press. Reproduced by permission of Taylor & Francis Books UK).

500 mg PO three times a day for 7 days is also adequate. Symptoms typically abate within 3 to 7 days. Other diagnosis including HIV infection should be considered in the absence of symptomatic improvement. Large ulcers may take several weeks to heal, and some may develop scarring. Suppurative lymphadenopathy requires prompt incision and drainage.[5]

Donovanosis (Granuloma Inguinale)

Granuloma inguinale or donovanosis refers to the same disease producing anogenital ulcerations. *Klebsiella granulomatis* is the causative bacteria. The infection is rare in the United States. It can be endemic in tropical and subtropical regions particularly in developing areas. Transmission occurs via direct contact between the bacteria and mucus membranes typically during sexual activity. The infection can be transmitted from mother to infant during vaginal delivery. Lesions form in these areas of entry up to 90 days after contact. They evolve into ulcerated, hypertrophic, necrotic, or sclerotic lesions (►**Fig. 4**). Inguinal lymphadenopathy can proceed to form subcutaneous granulomas known as *psuedoboboes*. Dissemination to abdominal organs, bones, and the mouth has been described.

The diagnosis is established by gently scraping the ulcer/lesion surface with a cotton swab. The specimen is mounted onto a glass slide. This preparation can be immediately stained and analyzed under a microscope or first fixed in alcohol. Donovan bodies are the characteristic dark staining oval or rod-shaped intracellular inclusion bodies. They are plentiful in afflicted individuals. A smear from a punch biopsy can also be performed. Culture, PCR, and serologic tests may be useful but are not widely available.

The CDC recommends treatment with doxycycline 100 mg PO BID for at least 3 weeks, or until all lesions are completely healed. Treatment has been shown to stop progression of the lesions. Healing occurs from the outer edges of the ulcer progressing inward. Pregnant and lactating women should be given erythromycin 500 mg PO QID instead.[6]

Lymphogranuloma Venereum

Chlamydia trachomatis infection underlies this clinical syndrome. Microtrauma of the skin and mucous membranes permits inoculation. This infection produces a primary genital lesion. Lymphangitis and lymphadenitis supervene in the drainage distribution of the inoculation site. The incubation period varies between 3 and 30 days for the primary phase and up to 6 months for the secondary stage.

LGV infection may be asymptomatic. Overt symptoms include fever, chills, headache, anorexia, myalgias, and arthralgias. A painless erosion or ulceration may form at the site of inoculation. Leukocytosis may be present. LGV can cause inflammation of the rectum with hyperplasia of the intestinal and perirectal lymphatics. Hemorrhagic proctitis may ensue. Proctoscopy may demonstrate nonspecific inflammation resembling ulcerative colitis. Ulcerations and inflammation are limited to the distal 10 cm in LGV proctitis.

Fig. 4 Perianal ulcerated lesion secondary to donovanosis (Photo—X. Delgadillo).

Fluctuant buboes associated with lymphadenopathy and anorectal ulcers accompany progression to the second stage of LGV infection. Secondary manifestations include sinuses, fistulas, and cicatricial deformities of the penis, urethra, or anorectal regions. Anal stenosis has been described. LGV should be considered and excluded as an etiology in MSM presenting with signs and symptoms of inflammatory bowel disease[7] (►**Fig. 5**).

Fibrosis, obliteration of lymphatic drainage, and strictures are seen in the third and final stages. Associated anorectal abscesses, ischiorectal and rectovaginal fistulas, as well rectal strictures from fibrosis may follow. Hemorrhoids enlarge secondary to fibrosis within the perirectal lymphatics. Granulomas, fistulae, and fibrotic strictures may be evident on endoscopy in patients with longstanding disease.

Fever and malaise are common during stages, wherein fibrosis and obstruction of lymphatics are operant. Severe pain is associated with lymphadenopathy. It may be unilateral and associated with edema and erythema of the skin overlying affected lymph nodes. One-third of affected lymph nodes rupture. Two-thirds slowly involute. This combination of sequelae creates an inflammatory mass of the inguinal and femoral lymph nodes separated by the inguinal (Poupart's) ligament. This constellation of physical findings produces the

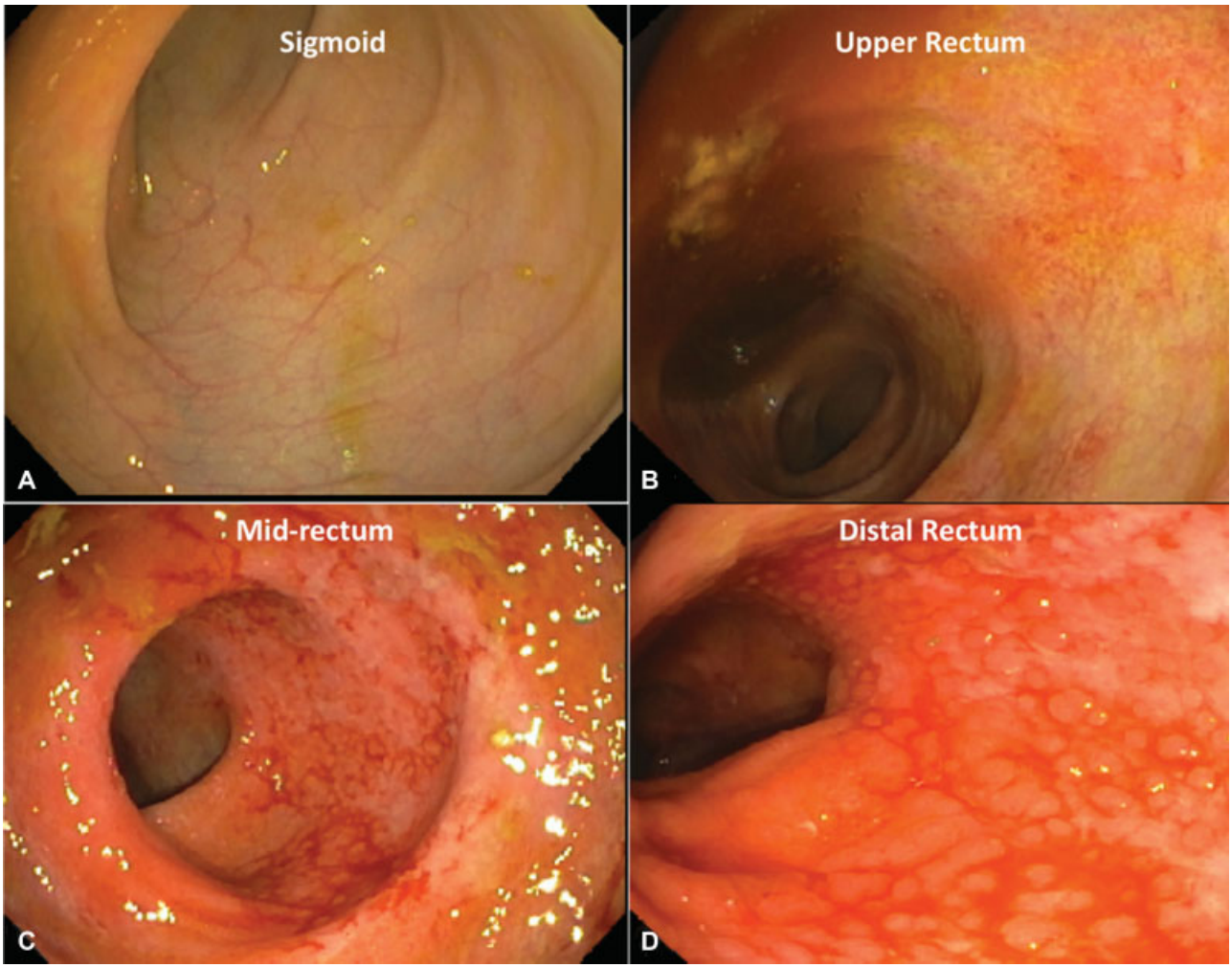

Fig. 5 Lymphogranuloma venereum (LGV) proctitis typically involves the last 12 cm of the hindgut. (**A**) A normal sigmoid is in evidence. (**B**) The mucosal vascular pattern is lost in the upper rectum. (**C**) Petechiae and friability are seen in the mid-rectum. (**D**) Atypical cobblestoning is evident in the distal rectum. Polymerase chain reaction (PCR) confirms LGV versus inflammatory disease in at-risk patients (Photos—A. Ortega).

classic *groove sign* associated with LGV infection (►**Fig. 6**). Deep inguinal node involvement is common and may progress to pelvic mass formation. Genital elephantiasis can develop 1 to 20 years following an untreated primary LVG infection.

PCR evaluation for *Chlamydia* is the most sensitive and specific diagnostic test. Cultures are only positive in 60 to 80% of cases. Cross-sectional imaging (computed tomography or magnetic resonance imaging) in LGV anorectal infection may show significant pelvic lymphadenopathy. Biopsy of

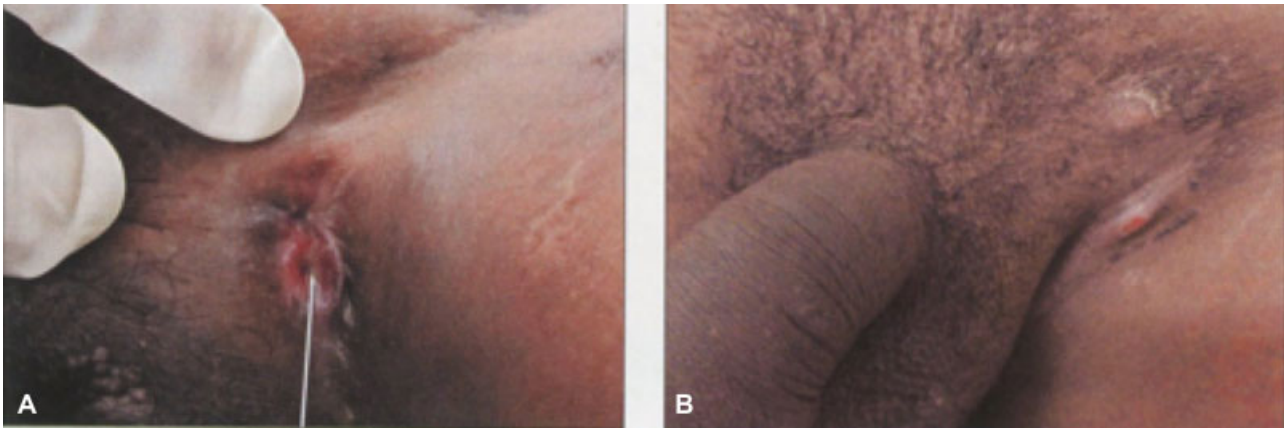

Fig. 6 Lymphogranuloma venereum: (**A**) perianal ulcer (**B**) inguinal groove sign (Photo—Genital & Perianal Diseases—A Color Handbook. Mroczkowski TF, Millikan LE, Parish LC, editors. 2014 © Boca Raton, FL: CRC Press. Reproduced by permission of Taylor & Francis Books UK).

Table 1 Summary of the clinical characteristics, evaluation, and treatment of anorectal syphilis, gonorrhea, chancroid, donovanosis, and lymphogranuloma venereum

	Syphilis	Gonorrhea	Chancroid	Donovanosis	LGV
Microbe	*Treponema pallidum*	*Neisseria gonorrheae*	*Haemophilus ducreyi*	*Klebsiella granulomatis*	*Chlamydia trachomatis*
One presentation	Painful or painless chancre—fissure-like but unusual locations	Thick mucopurulent discharge per rectum (urethra or vagina)	Painful anogenital ulceration	Anogenital ulceration	Erosion or ulceration at inoculation site
Associated signs and symptoms	Proctitis, rectal masses, lymphadenopathy	Itching, painful defecation, tenesmus, urethritis	Inguinal lymphadenopathy	Inguinal lymphadenopathy	Fever, chills, headache, anorexia, myalgias and arthralgias
Adjunctive diagnostic tests	Dark field examination, fluorescent treponemal antibody absorption test, microhemagglutination assay, VDRL/RPR	Intracellular gram-negative diplococci (Thayer-Martin plate)	PCR	Donovan bodies on microscopic examination, culture, PCR, and serologic tests	PCR
First-line treatment	PCN G 2.4 million units	Ceftriaxone 250 mg IM and anti-chlamydial treatment with azithromycin	Azithromycin 1 g PO or ceftriaxone 250 mg IM	Doxycycline 100 mg PO BID	Doxycycline 100 mg PO BID
Alternative of second-line treatment(s)	Doxycycline tetracycli-neerythromycin	Doxycycline in setting of azithromycin allergy	Ciprofloxacinerythro-mycin	Erythromycin	Erythromycin
Sequelae (untreated)	Secondary and tertiary syphilis	Tenosynovitis, septic arthritis, Fitz-Hugh-Curtis syndrome, pericarditis, meningitis, ARDS	Buboes, suppurative lymphadenopathy	Pseudobuboes dissemination to abdominal organs, bones, and mouth	Hemorrhagic proctitis, sinuses, fistulas, anorectal stenosis, penile, and urethral scarring/deformities, pelvic mass, genital elephantiasis

Abbreviations: ARDS, acute respiratory distress syndrome; BID, two times a day; IM, intramuscular; PCN, penicillin; PCR, polymerase chain reaction; RPR, rapid plasma reagin; PO, by mouth; VDRL, venereal disease research laboratory.

enlarged lymph nodes reveals necrosis with surrounding epithelioid and endothelial cells. These may also break down causing abscesses.

Spontaneous remission is common. Persistent infection is associated with disabling sequelae including fistulas, rectal stricture, and genital elephantiasis. Early treatment is preferable consisting doxycycline (100 mg PO BID for 21 days) or erythromycin (500 mg PO QID for 21 days) (►**Table 1**).[8]

Conflict of Interest
None.

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